CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-941

PHARMACOLOGY REVIEW

Review and Evaluation of Pharmacology and Toxicology Data

Key Words: **Antiviral; Herpes Labialis**

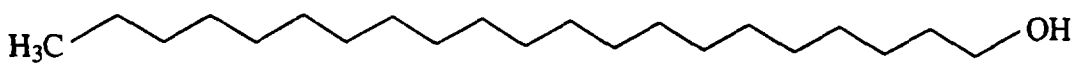
Reviewer: Lynnda Reid, Ph.D.
Division: Dermatologic and Dental Drug Products, HFD-540
Date: November 1, 1999

NDA No: NDA 20-941 - Addendum
Date: March 18, 1999

Information to Sponsor: Yes (x) No ( )

Sponsor: AVANIR Pharmaceuticals
9393 Towne Centre Drive, Suite 200
San Diego, CA 92121
(619) 558-0364

Drug: LIDAKOL®, 10% Cream
Code Name:
Generic Name: *n*-Docosanol, Behenyl Alcohol
Trade Name: Lidakol
Chemical Name(s):
CAS Number: 661-19-8.
Molecular Formula: 326.61
Molecular Weight: $C_{22}H_{46}O$
Structure:



Description: Waxy, white solid, insoluble in water.

Relevant IND and NDA Submissions: [redacted]

Drug Class: Anti-viral

Indication: Oral-Facial Herpes Simplex

Clinical Formulation:

Component	% w/w
n-Docosanol	10.0
Propylene Glycol,	[redacted]
Benzyl Alcohol,	
Sucrose Stearate (&) Sucrose Distearate	
Light Mineral Oil	
Purified Water,	

Route of Administration: Topical cream packaged in 1, 2, 5 and 15 gram tubes.

Proposed Clinical Protocol or Use: The upper estimate of the anticipated daily dose of n-docosanol for treatment of oral herpes is 0.5 to 1.0 mg/kg body weight (5 applications of 50 to 100 mg 10% n-docosanol cream per 50 kg body weight). The clinical endpoint is complete resolution of herpes lesions, and the prescribed maximum time of usage for a single episode is 10 days.

BACKGROUND

To be consistent with the requirement of drugs reviewed and approved in HFD-540 for chronic use, and due to the pharmacologic action of n-docosanol on cell membrane structures and its use on areas exposed to the sun, the Sponsor was asked to commit to dermal and photo-cocarcinogenicity studies during Phase 4 of development. At the post-NA meeting held on March 15, 1999, Avanir was informed that the only reason they were allowed to proceed with an NDA without addressing the issues of dermal carcinogenicity and photo-cocarcinogenicity potential prior to filing was in honor of the previous communications regarding carcinogenicity studies with HFD-530. They verbally acknowledged this request although a written commitment has not been received.

All other nonclinical issues communicated in the December 22, 1998 NA letter have been satisfied

CONCLUSION

From a Pharm/Tox perspective, NDA 20-941 is appovable provided the Sponsor gives a commitment to conduct Phase 4 dermal carcinogenicity and photo-cocarcinogenicity studies to assess the long-term effects of this drug product for a chronic indication.

/S/ 11-1-99

Lynnda Reid, Ph.D. Date
Pharmacologist/Toxicologist

cc:
NDA 20-941
HFD-540
HFD-540/Pharm/Reid
HFD-540/Pharm/Jacobs

For Concurrence Only:
HFD-540/DD/JWilkin /S/ 11/2/99 DFS
HFD-540/TL/AJacobs 11/2/99 for DFS

MAY 26 1998

Review and Evaluation of
Pharmacology and Toxicology Data
Division of Dermatologic and Dental Drug Products (HFD-540)

NDA 20-941 LIDAKOL®, 10% Cream

Drug: *n*-Docosanol, Behenyl Alcohol
Category: Anti-viral
Indication: Oral-Facial Herpes Simplex

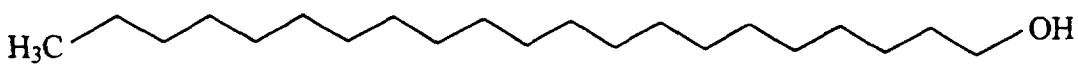
Sponsor: [redacted]

Number of Volumes: 16 (Vols. 2.1 and 1.3-1.17)
Date CDER Received: December 22, 1997
Date Assigned: January 9, 1998
Fileability Review Completed: January 15, 1998
Date 1st Draft Completed: May 13, 1998
Date Review Accepted by Supervisor: May 26, 1998

Chemical Names: *n*-Docosanol; Behenyl alcohol. CAS no. 661-19-8.

Physical and Chemical Characteristics:
Empirical Formula: $C_{22}H_{46}O$
Molecular Weight: 326.61
Description: Waxy, white solid, insoluble in water.

Structure:



Formulation and Route of Administration: Topical cream packaged in 1, 2, 5 and 15 gram tubes.

Clinical Formulation:

Component	% w/w
n-Docosanol	10.0
Propylene Glycol,	
Benzyl Alcohol,	
Sucrose Stearate (&) Sucrose Distearate	
Light Mineral Oil,	
Purified Water,	

Quantitative Composition of LIDAKOL Creams used in Nonclinical Studies:

Component (% w/w)	Formulation 1*	Formulation 3**
n-Docosanol	10	10
Propylene Glycol,		
Benzyl Alcohol,		
Sucrose Stearate (&) Sucrose Distearate		
Light Mineral Oil,		
Purified Water,		

* Formulation 1

** Formulation 3 is identical to the proposed clinical formulation and was used to make up the 10, 12 and 20% n-docosanol Creams used in the nonclinical studies

Review Index:

INTRODUCTION

LIDAKOL® 10% Cream is being developed to treat recurrent Oral-Facial Herpes Simplex. LIDAKOL is a highly lipophilic compound and, as such, may be effective in exerting inhibitory activity for viruses which are lipid-enveloped and utilize this property to gain entry into target cells via membrane fusion.

The upper estimate of the anticipated daily dose of n-docosanol for treatment of oral herpes is 0.5 to 1.0 mg/kg body weight (5 applications of 50 to 100 mg 10% n-docosanol cream per 50 kg body weight). The clinical endpoint is complete resolution of herpes lesions, and the prescribed maximum time of usage for a single episode is 10 days.

Associated IND Number: [redacted]

NONCLINICAL PHARMACOLOGY AND TOXICOLOGY STUDIES

Index of Submitted Nonclinical Studies:

No.	Pharmacodynamic Studies	Report No. (GLP *)	NDA Vol/Page	Rev. Page
1	1-Docosanol Inhibition of Enveloped Viruses: Mode of Action Studies - i. Effects of 1-Docosanol on Enveloped Viruses Entering Cells by Receptor-mediated Endocytosis. ii. Effects of Multiplicity of Infection (MOI) on the Antiviral Activity of 1-docosanol Against Selected Enveloped Viruses That Enter Cells by Receptor-mediated Endocytosis.	[redacted]	1.4/143 1.4/150	10
2	Studies on Mechanism of Viral Inhibitory Activity of LIDAKOL: a) Temporal-Relationship of Target Cell Treatment and Antiviral Activity of LIDAKOL. b) Binding and Uptake of LIDAKOL by Vero Cells. c) Study on LIDAKOL Effects on Viral Entry into Target Cells. d) Effect of LIDAKOL on HSV Receptors on Vero Cells. e) Effect of LIDAKOL on Replication of HSV. f) LIDAKOL Exhibits Preferential Inhibitory Activity for Lipid-Enveloped Viruses.	 LIDAK 105 LIDAK 106 LIDAK 107 LIDAK 108 LIDAK 109 LIDAK 110	 1.4/106 1.4/111 1.4/116 1.4/121 1.4/129 1.4/137	10
3	Verification of Binding Specificity of Radiolabeled HSVOI for Vero Cells.	LIDAK 112	1.4/126	10
4	Further Studies on the Temporal Relationship of Target Cell Treatment and Antiviral Activity of n-Docosanol.	LIDAK 120	1.4/196	10
5	The Anti-herpes Simplex Virus (HSV) Activity of n-Docosanol Includes Inhibition of the Viral Entry Process.	LIDAK 118	1.4/155	10
6	Anti-herpes Simplex Virus Activity of n-Docosanol Correlates with Intracellular Metabolic Conversion of the Drug.	LIDAK 119	1.4/184	10
7	Evaluation of LIDAKOL Suspensions in *in vitro* Herpes Simplex Virus.	LIDAK 102	1.4/046	10
8	Evaluation of LIDAKOL Suspension in *in vitro* Infectivity of Acyclovir-resistant HSV.	LIDAK 103	1.4/055	10
9	Effect of LIDAKOL on clinical isolates of HSV.	LIDAK 104	1.4/087	10

No.	*Pharmacodynamic Studies (Cont'd)*	*Report No. (GLP*)*	*NDA Vol/Page*	*Rev. Page*
10	Antiviral Effects of n-Docosanol Against Acyclovir-resistant Herpes Simplex Virus Type 1, Human and Murine Cytomegalovirus, Varicella-zoster Virus, Human Herpes Virus 6, Influenza A Virus, LP-BM5 Murine Retro virus, Vaccinia Virus, Adenovirus, and Reovirus.	LIDAK 117	1.4/061	11
11	Comparison of n-Docosanol Cream [redacted] Formulations with Acyclovir Ointment for Inhibitory Activity on Cutaneous Herpes Simplex Virus (HSV) Infections in Hairless and Hartley Guinea Pigs.	LIDAK 115	1.4/005	11
12	Evaluation of LIDAKOL Cream Activity in Cutaneous HSV-Induced Lesions in Guinea Pigs.	LIDAK 101	1.4/019	11
13	The Influence of Topical LIDAKOL on Herpes Virus-induced Cutaneous Lesions in Hairless Guinea Pigs.	LIDAK 113	1.4/024	11
14	Reevaluation of the Stearic Acid Containing Placebo and Characterization of the PEG Placebo in the HSV-2/Hairless Guinea Pig Model System.	LIDAK 116	1.4/028	11
15	[redacted] Safety Pharmacology: 1) Irwin Test in Mice Including Body Temperature Alterations 2) Spontaneous Motor Activity in Mice. 3) Barbiturate Induced Sleeping Time in Mice. 4) Proconvulsive Activity (Pentylenetetrazol Induced) in Mice. 5) Cardiovascular and Respiratory Parameters in the Anaesthetized Rat. 6) Charcoal Meal Transit in the Rat Small Intestine. 7) Urinary Output in Rats.	Toxicol * GOC/10/PH GOC/11/PH GOC/12/PH GOC/13/PH GOC/14/PH GOC/15/PH GOC/16/PH	 1.5/056 1.5/089 1.5/117 1.5/145 1.5/174 1.5/220 1.5/247	12
16	A General Pharmacology Study of n-Docosanol. [Addendum: Determination of Docosanoic Acid Using GC/NCI-MS.]	Grelan 48BL-20	1.5/003 1.5/048	14

No.	**ADME and Pharmacokinetic Studies**	Report No. (GLP*)	NDA Vol/Page	Rev. Page
17	The Absorption, Distribution, Metabolism and Excretion of n-[1-^{14}C] Docosanol 10% Cream (LIDAKOL™) Formulation 3 Following Oral Gavage to Rats.	LIDAK A100	1.15/096	16
18	The Absorption, Distribution, Metabolism and Excretion of n-[1-^{14}C] Docosanol 10% Cream (LIDAKOL™) Formulation 3 Following Oral Gavage to Rats.	LIDAK A101	1.15/101	16
19	The Absorption, Distribution, Metabolism and Excretion of n-[1-^{14}C] Docosanol 10% Cream (LIDAKOL™) Formulation 3 Following Oral Gavage to Rats.	LIDAK A102	1.15/118	16
20	Comparison of the Absorption of n-[1-^{14}C]Docosanol Formulated in LIDAK Cream Formulation 3, [redacted] Following Oral Gavage to Rats.	LIDAK A103	1.15/139	16
21	n-[^{14}C]Docosanol: Oral Absorption, Distribution, Metabolism and Excretion Study in the Rat.	[redacted]	1.15/154	18
22	Blood Levels of n-[^{14}C]Docosanol and Metabolites Following Dermal Application of LIDAKOL Cream Formulation 3 to Mice.	B101	1.15/002	19
23	Absorption and Pharmacokinetics of n-[1-^{14}C]Docosanol after Dermal Application to Rabbits (Preliminary & Definitive Phases).	[redacted]	1.15/013	20

No.	**Acute and Repeat Systemic Toxicology Studies**	Report No. (GLP*)	NDA Vol/Page	Rev. Page
24	Acute Oral Toxicity Study with LIDAKOL in Rats.	[redacted]255576*	1.6/035	22
[redacted]				
26	A 26-Week Daily Oral Toxicology Study of n-Docosanol Suspensions in Rats including Toxicokinetic Assessments.	LAK008*	1.7/133	23
[redacted]				
28	A 26-Week Oral Toxicity Study of n-Docosanol Suspension in Beagle Dogs Including Toxicokinetic Assessments.	LAK006*	1.10/002	26

No.	Acute and Repeat Topical Toxicology Studies	Report No. (GLP*)	NDA Vol/Page	Rev. Page
29	Acute Dermal Toxicity Study with LIDAKOL Cream in Rats.	[redacted]255587*	1.6/002	28
30	Primary Skin Irritation/Corrosion Study with LIDAKOL and LIDAKOL Placebo in the Rabbit (4-Hour Semi-Occlusive Application).	[redacted]087547*	1.6/071	28
31	Primary Skin Irritation Study with LIDAKOL Cream in Rabbits (4-Hour Semi-Occlusive Application).	[redacted]225598*	1.6/090	28
32	Primary Eye Irritation Study with LIDAKOL in Rabbits.	[redacted]255600*	1.11/159	29
33	Primary Eye Irritation Study with LIDAKOL Suspension in Rabbits.	[redacted]255622*	1.11/189	29
34	Screening for Eye Irritancy Potential using the Bovine Eye / Chorioallanoic Membrane (BECAM) Assay with LIDAKOL Cream.	[redacted]170054*	1.12/074	29
35	Acute Eye Irritation/Corrosion Study with LIDAKOL in the Rabbit.	[redacted]107505*	1.11/141	30
36	Contact Hypersensitivity to LIDAKOL Cream in Albino Guinea Pigs Maximization Test.	[redacted]255611*	1.11/024	30
37	Assessment of Contact Hypersensitivity to LIDAKOL in Albino Guinea Pig (Maximization Test).	[redacted]107516*	1.11/002	31
38	Phototoxicity Study of 10% n-Docosanol Cream (LIDAKOL) in the Guinea Pig.	LAK013*	1.11/067	31
39	Photosensitivity Study of 10% n-Docosanol Cream (LIDAKOL) in the Guinea Pig.	LAK014*	1.11/096	32
40	A 13-week Toxicity Study by Dermal Application of n-Docosanol Cream (LIDAKOL®) to CD-1 Mice Including Toxicokinetic Assessments.	LAK018*	1.6/120	33
41	Subacute 28-Day Repeated-Dose Dermal Toxicology Study on Intact and Abraded Skin in Rabbits.	[redacted]270382*	1.9/002	34
42	Subacute 28-Day Dermal Tolerance Study with n-Docosanol (LIDAKOL) by Daily 6 Hours Administrations to the Intact and Abraded Skin of Rabbits.	[redacted]107527*	1.8/268	36
43	A Penile Irritation Study in Rabbits with n-Docosanol 10% Cream and n-Docosanol 12% Cream.	SLS 3333.4*	1.12/002	37
44	A Vaginal Irritation Study in Rabbits with n-Docosanol 10% Cream and n-Docosanol 12% Cream.	SLS 3333.3*	1.11/437	38
45	Rabbit Vaginal Toxicology Study (28-Day) with Gas Chromatographic Analysis of Plasma From LIDAKOL Treated Rabbits. Analytical Report GC Analysis of 1-Docosanol in Rabbit Plasma.	PH 427-LK-001-91*	1.11/221 1.11/273 1.11/277	39

No.	Reproductive and Developmental Toxicology Studies	Report No. (GLP*)	NDA Vol/Page	Rev. Page
46	An Oral Dose Range-finding Fertility and Pre- and Post-natal Development Study of n-Docosanol Suspension in Rats.	LAK003*	1.12/164	40
47	An Oral Dose Range-finding Embryo-Fetal Development Study of n-Docosanol Suspension in Rats.	LAK004*	1.12/097	41
48	A Combined Fertility, General Reproductive Performance, and Embryo-Fetal Development Study of Orally Administered n-Docosanol Suspension in Rats.	LAK009*	1.12/258	42
49	A Pre- and Post-natal Development Study of Orally Administered n-Docosanol Suspension in Rats.	LAK011*	1.13/002	43
[redacted]				
51	An Oral Dose Range-finding Study of n-Docosanol Suspension in Rabbits.	LAK005*	1.13/254	45
52	A Dose Range-finding Embryo-Fetal Development Study of Orally Administered n-Docosanol Suspension in Rabbits.	LAK007*	1.14/002	46
53	An Embryo-Fetal Development Study of Orally Administered n-Docosanol Suspension in Rabbits.	LAK010*	1.14/056	46
54	A Fertility and General Reproduction Study in Rabbits with n-Docosanol 12% Cream.	[redacted]3333.2*	1.14/159	47

No.	Genotoxicity Studies	Report No. (GLP*)	NDA Vol/Page	Rev. Page
55	Salmonella typhimurium Reverse Mutation Assay with LIDAKOL.	[redacted]170010*	1.14/237	48
56	Gene Mutation Assay in Chinese Hamster V79 Cells in vitro with LIDAKOL.	[redacted]170021*	1.14/270	49
57	Chromosome Aberration Assay in Chinese Hamster V79 Cells in vitro with LIDAKOL.	[redacted]170032*	1.14/295	49
58	Micronucleus Assay in Bone Marrow Cells of the Mouse with LIDAKOL.	[redacted]170043*	1.14/340	49

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PHARMACOLOGY STUDY REVIEWS

Pharmacodynamic Study Reviews

A more complete review of the studies discussed in the Pharmacodynamic section of this review may be found in the Microbiology Review. Only a brief summary review of the findings from these studies is included in this review to describe 1) the proposed 'mechanism of action'; 2) the effect of n-docosanol on the Herpes Simplex virus *in vitro* and *in vivo*; and 3) safety pharmacology in rodents.

For *in vitro* pharmacodynamic studies, n-docosanol was with polyethylene oxide-polypropylene oxide block copolymers, [redacted] The resulting suspensions consisted of uniformly distributed globular particles ranging from [redacted] microns with an average size of 1.0 microns. Vehicle controls for *in vivo* studies utilized the same inactive components and substituted either water or stearic acid for the n-docosanol.

Effect of n-Docosanol *in vitro* on Herpes Simples Virus:

Study 1 - 1-Docosanol Inhibition of Enveloped Viruses: Mode of Action Studies - Conducted by the [redacted]

I. Effects of 1-Docosanol on Enveloped Viruses Entering Cells by Receptor-mediated Endocytosis.

II. Effects of Multiplicity of Infection (MOI) on the Antiviral Activity of 1-Docosanol Against Selected Enveloped Viruses That Enter Cells by Receptor-mediated Endocytosis.

Study 2 - Studies on Mechanisms of Viral Inhibitory Activity of LIDAKOL:

a) Temporal Relationship of Target Cell Treatment and Antiviral Activity of LIDAKOL. [Lidak Study 105]

b) Binding and Uptake of LIDAKOL by Vero Cells. [Lidak Study 106]

c) Study on LIDAKOL Effects on Viral Entry into Target Cells. [Lidak Study 107]

d) Effect of LIDAKOL on HSV Receptors on Vero Cells. [Lidak Study 108]

e) Effect of LIDAKOL on Replication of HSV. [Lidak Study 109]

f) LIDAKOL Exhibits Preferential Inhibitory Activity for Lipid-Enveloped Viruses. [Lidak Study 110]

Study 3 - Verification of Binding Specificity of Radiolabeled HSVOI for Vero Cells. [Lidak Study 112]

Study 4 - Further Studies on the Temporal Relationship of Target Cell Treatment and Antiviral Activity of n-Docosanol. [Lidak Study 120]

Mechanism of Action: In the studies listed above, n-docosanol, the active ingredient in LIDAKOL, demonstrated inhibition of viral replication for several lipid enveloped viruses. Using radiolabeled n-docosanol, *in vitro* studies demonstrated that uptake and metabolism of n-docosanol were necessary for anti-viral activity. Following bioactivation, n-docosanol reportedly blocks fusion of lipid-enveloped viruses, e.g. HSV-1 and HSV-2, with cell membranes, thus inhibiting cellular entry, nuclear localization, and subsequent viral replication. The exact mechanism behind this inhibition is unknown, but it has been hypothesized that biophysical changes in target cell membranes, e.g. changes in membrane fluidity, may induce cellular resistance to fusion with these viruses.

Study 5 - Evaluation of LIDAKOL Suspensions in *in vitro* Herpes Simplex Virus. [Lidak Study 102]

Study 6 - Evaluation of LIDAKOL Suspension in *in vitro* Infectivity of Acyclovir-resistant HSV. [Lidak Study 103]

Study 7 - Effect of LIDAKOL on clinical isolates of HSV. [Lidak Study 104]

Study 8 - Antiviral Effects of n-Docosanol Against Acyclovir-resistant Herpes Simplex Virus Type 1, Human and Murine Cytomegalovirus, Varicella-zoster Virus, Human Herpes Virus 6, Influenza A Virus, LP-BM5 Murine Retrovirus, Vaccinia Virus, Adenovirus, and Reovirus. [Lidak 117]

Study 9 - The Anti-herpes Simplex Virus (HSV) Activity of n-Docosanol Includes Inhibition of the Viral Entry Process. [Lidak Study 118]

Study 10 - Anti-herpes Simplex Virus Activity of n-Docosanol Correlates with Intracellular Metabolic Conversion of the Drug. [Lidak Study 119]

Summary of in vitro Pharmacology Study Results: As a result of the failure of viral material to move to the nucleus, there is a significant inhibition of 1) detectable HSV core and envelope proteins; 2) the number of cells (↓ by 68%) expressing the immediate early protein, ICP-4; and 3) viral production as judged in secondary plaque assays. Optimal activity *in vitro* requires incubation of cells with n-docosanol for several hours prior to HSV exposure.

In cells incubated with 7.5 mM radiolabeled n-docosanol prior to HSV inoculation, there was a 73% decrease in radioactivity in isolated nuclei as compared to untreated and control treated cells. This closely corresponds to the decrease in HSV plaque-formation generally observed with 18 mM n-docosanol. The ID50 (50% inhibitory dose) is approximately 12 mM.

The drug was found to be equally effective against wild type, clinical isolates and acyclovir resistant mutants of HSV. Other viruses which have been shown to be inhibited by n-docosanol include Varicella zoster virus, Herpes virus 6, Respiratory Syncytial Virus, Cytomegalovirus, Influenza A, HIV-1, Semliki Forest Virus and LP-BM-5 (Murine) Virus. Resistant viruses include Reovirus, Adenovirus (Type I), Poliovirus, Vaccinia Virus, and Vesicular stomatitis Virus.

In summary, n-docosanol *in vitro* -

- has no direct viricidal activity or loss of infectivity;
- does not interfere with binding of herpes virus to HSV-specific receptors;
- significantly inhibits cell wall translocation (viron-associated regulatory protein - VP16 transactivator); and
- significantly inhibits viral localization to cell nuclei.

Effect of n-Docosanol *in vivo* on Herpes Simples Virus:

Study 11 - Comparison of n-Docosanol Cream [redacted] Formulations with Acyclovir Ointment for Inhibitory Activity on Cutaneous Herpes Simplex Virus (HSV) Infections in Hairless and Hartley Guinea Pigs. [Lidak Study 115]

Study 12 - Evaluation of LIDAKOL Cream Activity in Cutaneous HSV-Induced Lesions in Guinea Pigs. [Lidak Study 101]

Study 13 - The Influence of Topical LIDAKOL on Herpes Virus-induced Cutaneous Lesions in Hairless Guinea Pigs. [Lidak Study 113]

Study 14 - Reevaluation of the Stearic Acid Containing Placebo and Characterization of the PEG. [Lidak Study 116]

Summary of in vivo Pharmacology Study Results: Efficacy of n-docosanol 10% cream against HSV-1 and HSV-2 induced cutaneous lesions was examined in hairless and Hartley guinea pigs. Adult guinea pigs were inoculated on the back (6-8 sites/animal) with 1 x 10^6 PFU/site using cutaneous puncture with a tattoo pen set at a depth of 2 mm. Treatment was initiated either 2 or 48 hours post inoculation with n-docosanol 10% (formulation 1), n-docosanol 10% in [redacted] 5% Acyclovir Ointment (positive control), or the appropriate vehicle control. Approximately 200 µl was applied with a glass rod with gentle circular rubbing t.i.d. When applied 2 hours after inoculation, n-docosanol 10% was shown to inhibited vesicle formulation. When first applied 48 hours after inoculation to established vesicles, n-docosanol appeared to significantly hasten disease resolution.

Safety Pharmacology Studies:

Study 15 - Safety Pharmacology: Conducted by [redacted] under GLP conditions, study dates: 12/6/95 through 1/19/96.

(1) Irwin Test in Mice Including Body Temperature Alterations. [Toxicol GOC/10/PH]
(2) Spontaneous Motor Activity in Mice. [Toxicol GOC/11/PH]

Study Designs: CD-1 male mice (6/group, ages 6-8 weeks) were treated with 0, 20, 200 or 2000 mg/kg n-docosanol suspended in [redacted] in water. Doses were administered by oral gavage at volumes of 20 ml/kg. Animals were evaluated for pharmacologic effects at 2 hours post n-docosanol dosing. Chlorpromazine (10 mg/kg) served at the positive control for suppression of spontaneous motor activity.

Summary of Study Results: Oral administration of doses up to 2000 mg/kg n-docosanol had no significant systemic pharmacologic effects on clinical behavior, body temperature, or spontaneous motor activity.

(3) Barbiturate Induced Sleeping Time in Mice. [Toxicol GOC/12/PH]
(4) Proconvulsive Activity (Pentylenetetrazol Induced) in Mice. [Toxicol GOC/13/PH]

Study Designs: CD-1 male mice (6/group, ages 6-8 weeks) were treated with 0, 20, 200 or 2000 mg/kg n-docosanol suspended in [redacted] in water. Doses were administered by oral gavage at volumes of 20 ml/kg. Two (2) hours following oral dosing, animals were dosed i.p. with either hexobarbitone (80 mg/kg) to evaluate barbiturate induced sleeping time, or pentylenetetrazol (30 mg/kg) to evaluate any proconvulsive activity of n-docosanol. Chlorpromazine (10 mg/kg) served as the positive control for time to loss of righting reflex and induced sleeping time, while caffeine (150 or 250 mg/kg) served as the positive control for proconvulsive activity.

Summary of Study Results: Oral administration of doses up to 2000 mg/kg n-docosanol had no systemic pharmacologic effects on hexobarbitone induced time to loss of righting reflex or sleeping

time, and proconvulsive activity in pentylenetetrazol treated mice. Positive controls reacted as expected.

(5) Cardiovascular and Respiratory Parameters in the Anaesthetized Rat. [Toxicol GOC/14/PH]

Study Designs: This study was designed to assess the effect of administration of n-docosanol on arterial blood pressure, heart rate, ECG and respiration and to determine the effect on the responses to acetylcholine and noradrenaline, in the anaesthetized rat. Crl:CD(SD)BR(VAF+) rats (6/group) were treated with 0, 250, 500 or 2000 mg/kg n-docosanol suspended [redacted] in water. Doses were administered by oral gavage at volumes of 20 ml/kg. Forty-five minutes following oral dosing, animals were anaesthetized with an intraperitoneal injection of 30 mg/kg sodium pentobarbitone and 1 g/kg urethane. Surgical preparation of the animals was performed for measurement of blood pressure (systolic, diastolic, mean), heart rate, ECG (QRS amplitude, PR interval) and respiration (rate and flow). Approximately 90-120 minutes after administration of the vehicle or n-docosanol the peak response of each parameter was measured before and after intravenous administration of noradrenaline (NA), and then similarly before and after intravenous administration of acetylcholine (ACh) for a period of 50 minutes.

Summary of Study Results: There were no significant direct dose-related effects of n-docosanol against any measured parameter: blood pressure, heart rate, ECG and respiration.

(6) Charcoal Meal Transit in the Rat Small Intestine. [Toxicol GOC/15/PH]

Study Design: This study was designed to identify any activity of n-docosanol on the gastrointestinal tract using charcoal mean transit in the rat small intestine. Crl:CD(SD)BR (VAF+) rats (6/group) were treated with 0, 250, 500 or 2000 mg/kg n-docosanol suspended [redacted] in water. The positive control/standard was 50 mg/kg morphine. Doses were administered by oral gavage at volumes of 20 ml/kg to fasted animals. Two hours after dosing, 1 ml of a charcoal meal was administered orally to each animal. Animals were sacrificed 30 minutes later and the small intestines were removed. The distance the charcoal meal had traveled and the total length of small intestine were measured.

Summary of Study Results: As expected, administration of the standard, 50 mg/kg morphine, significantly ($p<0.01$) reduced the movement of the charcoal meal along the small intestine. Administration of n-docosanol had no effect on the mean transit times.

(7) Urinary Output in Rats. [Toxicol GOC/16/PH]

Study Design: This study was designed to assess the effect of n-docosanol on renal function by analysis of urine output. Crl:CD(SD)BR (VAF+) rats (6/group) were treated by oral gavage (10 ml/kg) with 0, 250, 500 or 2000 mg/kg n-docosanol suspended [redacted] in water. The positive control/standard was 20 mg/kg furosemide. Doses were administered 30 minutes after

administration of 20 ml/kg saline (food and water were withheld for two hours prior to saline dosing and for 6 hours after dosing). Urine was collected at 3, 6 and 23 hours after dosing, the volume recorded and samples analyzed for sodium (Na), potassium (K), chloride (Cl) and inorganic phosphate (Pi).

Summary of Study Results: As expected, furosemide caused significant ($p>0.001$) increases in urine volume and concentrations of Na, K and Cl 3 hours post dose and significant ($p>0.001$) decreases in Na and Cl 23 hours post dose. There were no changes in urinary output parameters in the n-docosanol treated rats during the 23 hours observed.

Study 16 - A General Pharmacology Study of n-Docosanol. [Addendum: Determination of Docosanoic Acid Using GC/NCI-MS.] Study Report no. 48BL-20. Conducted by [redacted] in accordance with Japanese Guidelines for General Pharmacology Studies.

Study Design: This general pharmacology study was designed to study the effect of n-docosanol on the central nervous system, autonomic system, respiratory and cardiovascular system, digestive system, renal system, and local anesthetic activity (corneal and cutaneous reflexes). n-Docosanol was administered to male ICR mice (21-31 g), male Sprague-Dawley rats (100 to 175 g), Beagle dogs (7-10 months, 9.0-9.3 kg), and male Hartley guinea pigs (6-8 weeks, 372-569 g) as follows: orally to male mice and rats at doses of 100, 300 and 1000 mg/kg; intravenously to dogs of either sex at doses of 0.1, 0.3, 1.0 and 3.0 mg/kg; and topically (ocular & dermal) to guinea pigs at 0.3, 1.0 and 3.0 % cream. In addition, an *in vitro* study with isolated guinea pig ileum was conducted with final concentrations of n-docosanol of 10^{-6}, 10^{-5} and 10^{-4} M added to the bathing fluid. n-Docosanol was suspended in aqueous [redacted] for oral administration, F-68 saline for i.v. injection, and in Tyrodes's solution for *in vitro* use. Control and inducing substances included hexobarbitol, phenobarbital, histamine, pentobarbital, charcoal, acetylcholine, diazepam, chlorpromazine, caffeine, atropine, lidocaine, pentylenetetrazole, aminopyrine, furosemide, and acetic acid.

Summary of Study Results: n-Docosanol at oral doses of $\leq$1000 mg/kg produced no significant effect on general or clinical behavior, locomotor activity, thiopental-induced sleeping time, synergistic or antagonistic convulsant activity, or intestinal charcoal transport in male mice (10-20/group). n-Docosanol had no significant effect on normal body temperature or urinary volume or electrolyte excretion in male rats (8/group).

Following i.v. administration to dogs (3), n-docosanol produced little or no effect on the respiratory rate, blood pressure, heart rate and ECG in anesthetized animals at doses $\leq$3 mg/kg.

Topical and ocular applications of $\leq$3.0 % n-docosanol did not demonstrate any local anesthetic activity in male guinea pigs (5-15/group). In the *in vitro* study, n-docosanol did not show any significant influence on the spontaneous movements of isolated guinea pig ileum (5) at $\leq 10^{-4}$ M, and it had little or no effect on acetylcholine-, histamine- or barium-induced contractions.

All positive controls responded appropriately.

Addendum: **Determination of Docosanoic Acid Using GC/NCI-MS**

This study was performed to examine the relationship between plasma concentrations of n-docosanol and it's major metabolite docosanoic acid. Male Sprague-Dawley rats (1/dose, ages 6-7 weeks, weighing 202.6 to 219.1 g) were administered doses of 30, 100, 300 and 1000 mg/10ml/kg n-docosanol suspended in aqueous solutions of [redacted] prepared by both [redacted] pharmaceuticals. Blood samples were collected in heparinized capillary tubes from a tail vain at 0.5, 1, 2, 4 and 8 hrs. Following centrifugation, 50 µl of plasma was diluted 1:1 with [redacted] water and stored at -20°C. For analysis, 100 µl diluted rat plasma were mixed with 200 µl of 0.1 M phosphoric acid and 50 µl of internal standard solution (eicosanoic acid 100 ng/ml ethanol) and the acids were extracted and then derivatized to corresponding PFB-esters with Na_2SO_4 and K_2CO_3 (1:1, Ca. 10 mg). After the esterfication, the reaction mixture was diluted with 2000 µl of n-hexane and centrifuged. The residue was redissolved in 100 µl of n-hexane and 1 µl of the resulting solution was subjected to GC/NCI-MS. GC separations were carried out with a RTX-1 chemically bonded fused silica capillary column with methane as the GC carrier gas. Column head pressure was held at 0.7 kg/cm2 and the flow rate was 1 ml/min. Column temperature, injection-port temperature and ion-source temperature were kept at 170, 280 and 200°C, respectively. The ionization energy and the trap current were maintained at 70 eV and 350 µA, respectively.

Summary of Study Results: n-Docosanoic acid concentrations found in rat plasma after a single oral administration of n-docosanol suspensions in aqueous [redacted] prepared by either [redacted] Pharmaceuticals are presented in Table PK-1a and PK-1b, respectively.

Table PK-1a: Determination of n-Docosanoic acid in rat plasma following a single oral administration of a n-docosanol suspension in aqueous [redacted] from solutions prepared by [redacted]

Time	Concentration of Docosanoic Acid (ng/ml)			
(hr)	30 mg/kg	100 mg/kg	300 mg/kg	1000 mg/kg
0.5	29.9	38.6	55.7	69.1
1	140.1	202.9	213.0	236.6
2	161.6	230.8	315.4	309.5
4	98.4	124.3	141.3	146.2
8	46.3	36.3	45.6	45.0

Table PK-1b: Determination of n-Docosanoic acid in rat plasma following a single oral administration of a n-docosanol suspension in aqueous [redacted] from solutions prepared by [redacted] Pharmaceuticals.

Time	Concentration of Docosanoic Acid (ng/ml)			
(hr)	30 mg/kg	100 mg/kg	300 mg/kg	1000 mg/kg
0.5	95.9	67.1	24.9	29.9
1	179.5	219.2	184.6	165.8
2	152.3	283.6	257.8	263.8
4	86.6	220.7	206.0	202.5
8	46.5	97.3	134.2	144.5

Review Notes: *From this data, it appears that n-docosanol is readily metabolized following absorption with absorption and/or metabolism of n-docosanol peaking between 1 and 4 hours. As observed in the previous studies looking at n-docosanol plasma levels, the relationship between the administered dose and the appearance of n-docosanoic acid in the plasma is non-linear and dose-dependent. There are no significant differences in the plotted area under the curve (AUC) following administration of the 300 and 1000 mg/kg doses for either preparation, however, exposure, as measured by AUC, does appear to be prolonged following administration of the [redacted] preparation. AUC calculations were not submitted and samples were only measured for 8 hours following administration. The Sponsor will be asked to provided the calculated AUC_{0-8} and any available information on n-docosanol plasma levels in these animals.*

Pharmacokinetic Study Reviews

In vitro Pharmacokinetic Studies: To investigate the uptake, distribution, and metabolism of n-docosanol by cultured cells, target cells were incubated with n-[^{14}C]docosanol. Most of the radiolabel (73%) was recovered in membranous fractions and <1% was associated with a nuclear fraction. Analysis by chemical (Vitride) reduction suggested that a significant portion of n-docosanol is oxidized to n-docosanoic acid and then incorporated as a acyl group on polar lipids. Up to 60% of the cell-associated radiolabel was incorporated into phospholipids that co-purified with phosphatidylcholine and phosphatidylethanolamine. The rate and extent of metabolic conversion of n-docosanol varied with the cell type and surfactant used to suspend the compound. The anti-HSV activity was quantitatively proportional to the amount of metabolism observed.

In vitro penetration of n-[1-^{14}C]docosanol formulations [Study LP-17339] was compared using human cadaver skin (Table PK-2). Less than 2.0 % of the radio-label from the proposed formulation (Formulation 3) penetrated the skin and less than 0.01 % was found in the reservoir fluid.

Table PK-2: 24 Hour Cumulative Mean ± SD Penetration [µg n-Docosanol (% dose)].

Sample	Formulation 1		Formulation 3	
Stratum Corneum	15.12 ± 4.770	(0.500 ± 0.160)	34.47 ± 32.98	(1.150 ± 1.100)
Epidermis	13.02 ± 6.810	(0.004 ± 0.002)	21.92 ± 18.63	(0.730 ± 0.620)
Dermis	0.630 ± 0.520	(0.020 ± 0.020)	1.280 ± 0.560	(0.040 ± 0.020)
Reservoir	0.111 ± 0.052	(0.004 ± 0.002)	0.083 ± 0.028	(0.003 ± 0.001)

Acute Oral ADME Studies:

Study 17 - The Absorption, Distribution, Metabolism and Excretion of n-[^{14}C]Docosanol 10% Cream (LIDAKOL™) Formulation 3 Following Oral Gavage to Rats. [Lidak Study A100, *in life:* 7/7/93 to 8/4/93.]

Study 18 - The Absorption, Distribution, Metabolism and Excretion of n-[^{14}C]Docosanol 10% Cream (LIDAKOL™) Formulation 3 Following Oral Gavage to Rats. [Lidak Study A101, *in life:* 10/23/93]

Study 19 - The Absorption, Distribution, Metabolism and Excretion of n-[^{14}C]Docosanol 10% Cream (LIDAKOL™) Formulation 3 Following Oral Gavage to Rats. [Lidak Study A102, *in life:* 1/27/94]

Study 20 - Comparison of the Absorption of n-[^{14}C]Docosanol Formulated in LIDAK Cream Formulation 3, [redacted] Following Oral Gavage to Rats. [Lidak Study A103, *in life:* 10/3/94]

Study Design: The oral ADME studies (17-20) were designed and conducted by LIDAK Pharmaceuticals, 11077 North Torrey Pines Road, La Jolla, CA, to investigate the absorption,

metabolism, and excretion of n-[1-^{14}C]docosanol and to provide data to evaluate the extent of exposure to n-docosanol from accidental oral ingestion following application to the lips. n-Docosanol (1-50 mg/rat) formulated at concentrations of 10% in cream (Formulation 3), [redacted] was administer to female [redacted] rats (~8 weeks in age, 1-3 rats/time point). Animals were fasted overnight prior to treatment and for 6 hours after treatment (water was available throughout the study period). Plasma, RBC fractions, tissues, urine and feces were analyzed at various time points between 0.2 hours and 32 days post-dosing for total radioactivity and metabolic products of n-docosanol. The percent of intact n-docosanol to metabolic products in plasma and tissues was determined by thin layer chromatography (TLC) following lipid extraction.

Summary of Study Results:

Absorption: The rate and amount of n-docosanol absorbed into the body through the gastrointestinal tract appeared to be similar between doses formulated in cream [redacted] Saturation of n-docosanol uptake was not observed and increasing plasma radioactivity was associated with increasing dosages of the drug over a 24 hour time period. Higher plasma levels were observed following oral administration of n-docosanol suspended [redacted] however, the observed kinetics of appearance and decline of plasma radioactivity was similar for all three formulations (Table PK-3).

Table PK-3: Comparison of systemic exposure (AUC_{0-24}) resulting from oral gavage of n-[1-^{14}C] docosanol 10% cream formulations to adult female rats weighing 194 ± 3.3 g.

Dose	Cream Formulation 3	1% Tween 80	Pluronic F-68
3 mg/kg	2.6 µg-eq.hr/ml	4.8 µg-eq.hr/ml	17.7 µg-eq.hr/ml
300 mg/kg	80.6	52.0	149.0

Distribution: Radioactivity was detected in the plasma within 0.5 hours, with significant levels detected at 1 hour and peak concentrations occurring between 6 and 12 hours following a single oral dose. Radioactivity was detected in all tissues examined within 1 day of dosing: intestine, stomach, gastrointestinal contents, liver, spleen, lung, heart, kidney, muscle, brain, brown fat and white fat. On day 1, the liver, spleen and brown fat contained the highest levels of radioactivity (Table PK-4). Within 24 hours post-dosing. over 90 % of the radioactivity in the liver was determined to be in the form of polar lipid metabolites. The half-life of n-docosanol derived radioactivity in the liver was 4-5 days. Similar rates of clearance were observed from the spleen. By day 32 post-gavage, most of the tissue-associated radioactivity had been eliminated, with only about 1% of the original dose localized in brown fat (primarily incorporated as triglycerides) and brain lipids.

Metabolism: Plasma samples from the 3, 6 and 12 hour time points were extracted and analyzed by TLC. At 3 hours n-docosanol accounted for 11% of the radioactivity, n-docosanoic acid 66%, and 23% remained at the origin as polar phosphatides. By 6 hours, only traces of n-docosanol could be detected and the n-docosanoic acid and polar phosphatides accounted for approximately 25% and 75% of the radioactivity, respectively. Metabolic conversion appeared nearly complete by 12 hours post-gavage when only slight traces of n-docosanol and n-docosanoic acid could be detected and the radioactivity migrated as polar phosphatides. The metabolic pathway appears similar to other fatty

alcohols: oxidation to fatty acids followed by esterfication to a wide variety of lipids, glycerides and phosphoglycerides which are then appear to be universally distributed in tissues.

Excretion: Approximately 29 to 90.6% of the administered radioactivity was detected in the feces at 24 hours and 76 to 93.2% at 72 hours post-dosing. Total recovery of radioactivity between feces and cage washings (primarily fecal and urinary products) accounted for 29.5-90.8% and 76.9-99.4% of administered dose at 24 and 72 hours, respectively. The Sponsor has estimated that 75-90% of the radioactivity in the feces is attributable to unabsorbed product.

Table PK-4: Tissue radioactivity levels following a single gavage administration of n-[1-^{14}C]docosanol 10% cream to adult female rats weighing 165-175 g.

Tissue	Day 1	Day 32
Liver	1.23 % dose/g tissue	0.010 % dose/g tissue
Spleen	0.52	0.013
White Fat	0.19	0.047
Brown Fat	0.57	0.083
Muscle	0.04	0.007
Brain	0.02	0.011
Heart	0.22	0.021
Lung	0.23	0.017
Kidney	0.18	0.016
Stomach	0.33	0.017
Intestine	0.49	0.031
Total Tissue	**13.3 % of total dose**	**1.07 % of total dose**
Total Tissue plus GI contents	**18.9 % of total dose**	**1.10 % of total dose**

Study 21 - n-[^{14}C]Docosanol: Oral Absorption, Distribution, Metabolism and Excretion Study in the Rat. Study Report No. LAK012. *In life:* 9/26/94 - 3/28/95, Conducted by [redacted] in accordance with internationally recognized Good Laboratory Practices.

Study Design: This study was designed to 1) determine the rate and extent of absorption by comparing urinary excretion of radioactivity after oral and intravenous administration; 2) investigate the time course of radioactivity in the blood; 3) examine the qualitative tissue distribution (including pregnant animals); and 4) determine the metabolite profile in urine, feces, and plasma following a single dose of n-[13-^{14}C]docosanol. Rats were administered 10 mg/kg labeled n-docosanol in [redacted] by oral gavage (18 males, 24 females, 20 non-pregnant and 4 pregnant) or 1 mg/kg labeled n-docosanol [redacted] by intravenous injection (6 males, 4 females). For autoradiography studies, pregnant females were dosed on day 18 of gestation.

Summary of Study Results: After i.v. doses, approximately 50% of the radioactivity was excreted in the expired air (presumably as $^{14}CO_2$), 2% in the urine, 1% in the feces, and 27% was present in the tissues at the time of sacrifice 168 hours postdosing (Table PK-5a). Following oral dosing over a period of 168 hours, approximately 79% of the radioactivity was found in the feces, 10% was

radioactivity recovered from tissue, plasma and urine at sampling time points is presented in Table PK-6. Systemic absorption of n-docosanol, <0.0003% of the applied dose, appears to be limited.

Table PK-6: Total ^{14}C counts (DPM) following dermal application of n-[1-^{14}C]docosanol to mice.

	265 mg/kg (4.47 X 10^9 DPM/kg) n-[1-^{14}C]Docosanol			213 mg/kg (5.14 X 10^9 DPM/kg) n-[1-^{14}C]Docosanol		
Time (hrs)	Cage Wipes (DPM-Bkgd)	Plasma (DPM-Bkgd/100 µl)	Plasma (ng.Equiv/ml)	Cage Wipes (DPM-Bkgd)	Plasma (DPM-Bkgd/100 µl)	Plasma (ng.Equiv/ml)
0.5	2 - 4	1 - 13	0.6 - 7.6	ND	ND	ND
1.0	0 - 5	3 - 12	1.8 - 7.0	ND	ND	ND
2.0	3 - 192	3 - 5	1.8 - 2.9	ND	ND	ND
4.0	11 - 292	4 - 8	2.3 - 4.7	ND	ND	ND
8.0	2 - 17	4 - 10	2.3 - 5.9	ND	ND	ND
24.0	6 - 13	1 - 8	0.6 - 4.7	17 - 135	54 - 60	22 - 24
48.0	ND	ND	ND	4 - 16	43 - 57	17 - 23
72.0*	33 & 65	10 & 11	5.9 & 6.5	19 & 53	42 & 50	17 & 20

* At 72 hours, only 2 animals were samples. All other time points represent a n of 3. Limit of detection - 10 ng/ml.. ND = No Data.

Study 23 - Absorption and Pharmacokinetics n-[^{14}C]Docosanol after Dermal Application to Rabbits (Preliminary & Definitive Phases). Study report no. 6634-100, *In life:* 5/18 to 6/21/95, Conducted by [redacted] in compliance with Good Laboratory Practices (21 CFR 58).

Study Design: A single dermal dose of n-[1-^{14}C]docosanol was administered to 12 male rabbits at a dose of 25 mg/kg over an area of approximately 43 cm^2 of nonabraded and abraded skin. Doses were removed 24 hours after application by rinsing. Rinse samples were retained for radioactivity analysis. Blood, skin, urine, feces and expired air were collected at various time points and assayed for radioactivity.

Summary of Study Results: Only a small percentage of the radiolabeled dose was excreted in the urine, feces, CO_2, and organic volatiles. Recovery of the radioactivity in the cage wash, cage wipe, urine, feces and expired air averaged 0.178% and 0.086% of the applied dose for animals with nonabraded and abraded skin, respectively. Cmax values were minimal and ranged from 0.004 µg eq/g to 0.011 µg eq/g (Table PK-7). Most of the applied radioactivity was recovered in the skin wash (>93%) (Table PK-8). Low but quantifiable levels of radioactivity were recovered as $^{14}CO_2$.

Table PK-7: Pharmacokinetic parameters for n-[1-^{14}C]docosanol-derived radioactivity in blood and plasma of rabbits receiving a single topical dose (25 mg/kg).

Parameter	Nonabraded Skin		Abraded Skin	
	Blood	Plasma	Blood	Plasma
C_{max} (µg.eq/g)	0.011	0.007	0.009	0.004
T_{max}	32	88	40	56
AUC_{0-last} (µg eq.hr/g)	1.28	1.02	1.04	0.649

Table PK-8: Percent of radioactivity observed at 168 hours post-dose for male rabbits following a single dermal application of n-[1-^{14}C]docosanol (25 mg/kg).

Sample	Nonabraded Skin	Abraded Skin
Occlusive Cover *	0.546 ± 0.762	0.083 ± 0.119
Enclosure Rinse	0.303 ± 0.114	0.566 ± 0.448
Cage Wash	0.008 ± 0.005	0.002 ± 0.002
Cage Wipe	0.010 ± 0.007	0.002 ± 0.001
Skin Wash *	93.69 ± 8.155	94.36 ± 2.052
Skin Test Site	1.713 ± 0.296	1.151 ± 0.261
Plasma	NQ	NQ
Urine	0.018 ± 0.003	0.018 ± 0.004
Feces	0.002 ± 0.003	NQ
CO2	0.136 ± 0.074	0.057 ± 0.034
Volatiles	0.004 ± 0.003	0.008 ± 0.007
Total Recovery	96.44 ± 9.321	96.24 ± 2.038
Total Absorbed **	**1.898 ± 0.359**	**1.231 ± 0.304**

* Collected at 24 hours post-dosing.

** Total radioactivity minus radioactivity from occlusive cover, enclosure rinse & skin rinse.

There were no significant differences between abraded and nonabraded skin. Absorption of the test material was minimal with most of the test material remaining on the surface of the skin.

TOXICOLOGY STUDY REVIEWS

Unless otherwise stated animals used in toxicology studies were all acclimatized prior to study initiation and randomized to treatment groups. Food and water were analyzed for impurities and were freely available unless otherwise stated.

Aqueous suspensions of n-docosanol for oral administration were prepared from a 20 % n-docosanol stock suspension in [redacted] prepared weekly or as needed. This suspension was used for high group dosing, while lower concentrations were prepared on the day of use by dilution of the 20 % suspension with [redacted] Quality control of dosing solutions was performed by [redacted] and unless otherwise stated, were found within protocol limits.

Acute and Repeat Systemic Toxicology Study Reviews (GLP)

Study 24 - Acute Oral Toxicity Study with LIDAKOL in Rats. Study report no. [redacted] 255576. *In life:* 10-27 to 11/10/89, conducted by [redacted] in accordance with OECD GLP guidelines. n-Docosanol batch no. 6232.

Summary Results: Administration of 2000 mg/kg n-docosanol suspended in olive oil to Wistar rats (5 animals/sex) by oral gavage did not result in any moralities or drug related clinical signs of toxicity during a 15 day post-dosing observation period. There were no macroscopic findings observed at necropsy.

[redacted]

[redacted]

Study 26 - A 26-Week Daily Oral Toxicology Study of n-Docosanol Suspensions in Rats including Toxicokinetic Assessments. Study report no. 94/LAK008/0963. *In life:* 12/14/94 to 6/19/95, conducted at [redacted] in compliance with OEDC GLP guidelines.

Study Design: CD rats (20/sex/group, ages 28-35 days) were treated by oral gavage with 0, 10, 100 and 1000 mg/kg/day n-docosanol suspended in [redacted] aqueous solutions for 26 weeks at a constant volume-dosage of 5 ml/kg. Animals were evaluated for the following: clinical signs of toxicity; changes in bodyweight and food intake; ophthalmoscopy (weeks 12 and 25); hematology and clinical (serum and urine) chemistry (weeks 13 and 26); and organ weights, gross necropsy, and microscopic tissue changes at study termination. All gross lesions and the following tissues were evaluated microscopically:

-adrenals *
-aorta (thoracic)
-brain *
-cecum
-colon
-duodenum
-epididymides
-esophagus
-eyes and optic nerves
-femur w/marrow
-heart *
-ileum
-jejunum
-kidneys *
-liver *
-lungs w/mainstem bronchi *
-lymph nodes (mandibular and mesenteric)
-mammary gland
-ovaries *
-pancreas
-pituitary *
-prostate *
-rectum
-salivary glands (submandibular)
-sciatic nerve (left)
-seminal vesicles
-skeletal muscle (thigh)
-spinal cord
-spleen *
-sternum
-stomach
-testes *
-thymus *
-thyroid and parathyroid *
-trachea
-urinary bladder
-uterus w/cervix *

* analysis included organ weight. Tissues preserved but not examined included the harderian glands, mammary gland (cranial), sciatic nerve (right) and tongue.

Samples for toxicokinetic evaluations were collected from the retro-orbital sinus at 0.5 1, 2, 4, 8, and 24 hours after dosing on day 1 and at the end of study weeks 13, and 26 from satellite animals assigned to treatment groups (10/sex/treatment group) and the vehicle control group (6/sex). Three treated animals or 2 control animals per sex/group/time point were preselected by numerical ordering and sampled at either 0.5 and 4 hours, 1 and 8 hours, or 2 and 24 hours. All satellite animals were discarded, without necropsy, after the completion of sampling in week 26 of treatment.

Statistical significance was defined as $p<0.05$. Statistical analyses were performed as follows:

Clinical laboratory results - Student's t-test
Organ weights and bodyweight - Bartlett's test, Behren-Fisher test and Dunnett's test.
Macroscopic and microscopic pathology - Fisher's Exact test.

Summary of Study Results: With two exceptions, there were no significant differences between groups in bodyweight, food intake, blood and urine profiles, and organ weights. No ophthalmic, macroscopic or microscopic pathological abnormalities were observed.

One female (#49), dosed at 100 mg/kg/day, died in week 25. At necropsy, the animal presented with moderate lung congestion and slight dilation of tracheal glands. The cause of death was thought to be the result of accidental aspiration of test material, unrelated to toxicity as a result of exposure to n-docosanol.

One male (#80), dosed at 1000 mg/kg/day presented with several abnormal clinical pathology parameters including increased (2 fold) kidney weights; slight anemia; high plasma urea, creatinine, cholesterol, phosphorus and triglyceride concentrations. However, since this was an isolated incidence, its relationship to n-docosanol was considered unlikely.

The no-effect level determined in this study was 1000 mg/kg/day.

[redacted]

Dose Verification: Analysis of 20% n-docosanol study suspensions by [redacted] resulted in levels ranging between [redacted]% w/w n-docosanol during the study period.

Review Comment: *Three plasma samples from control animals also had measurable n-docosanol levels: 1 male at 13 weeks of 16 ng/ml, and 1 male and 1 female at 26 weeks of 10 and 18 ng/ml, respectively. These levels are close to the limit of detection and may represent background, contamination, or errors in labeling or recording samples. Due to the negligibility of these readings and the absence of adverse effects at the highest doses administered, these results do not sufficiently impact*

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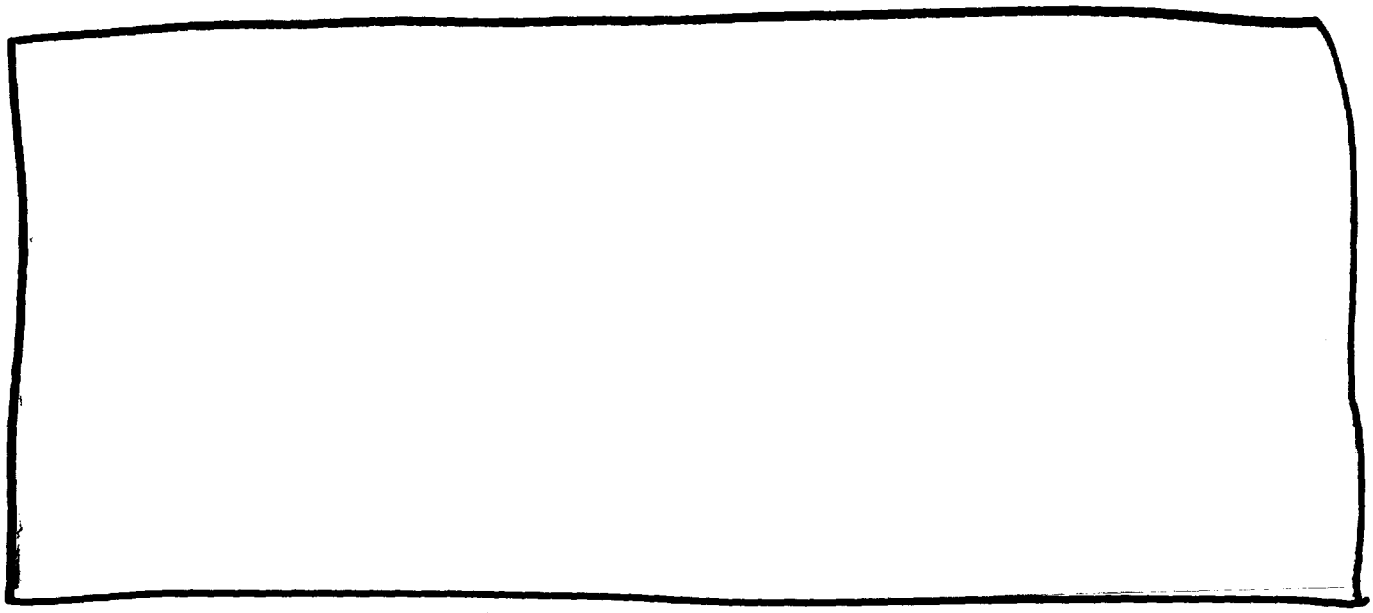

Study 28 - A 26-Week Oral Toxicity Study of n-Docosanol Suspension in Beagle Dogs Including Toxicokinetic Assessments. Study report no. 95/LAK006/0406. *In life:* 7/27/94 to 2/6/95, conducted at [redacted] with toxicokinetic sampie analyses performed by [redacted] in compliance with OEDC GLP guidelines. n-Docosanol batch no. 45228.

Study Design: Beagle dogs (4/sex/group, ages 19-23 weeks, 6.6 to 9.6 kg) were treated by oral gavage with 0, 20, 200 and 2000 mg/kg/day n-docosanol suspended in 1% Tween 80 aqueous solutions for 27 weeks. Animals were evaluated for clinical signs of toxicity; changes in bodyweight, food intake, ophthalmoscopy (weeks 11 and 24), hematology, plasma and urine chemistries, and organ weights, and gross and microscopic tissue changes. Samples for toxicokinetic evaluations were collected at 2, 4, 8, 12, 16 and 24 hours after dosing on day 1 and at the end of study weeks 13, and 26. Tissues preserved for histopathology include the following:

-adrenals *
-aorta
-brain *
-cecum
-colon
-duodenum
-epididymides
-esophagus
-eyes and optic nerves
-heart *
-ileum
-jejunum
-kidneys *
-liver *
-lungs w/mainstem bronchi *
-lymph nodes - axillary, mandibular and mesenteric
-mammary gland
-ovaries *
-pancreas
-pituitary *
-prostate w/urethra*
-rectum
-salivary glands (submandibular)
-sciatic nerve (left)
-skeletal muscle (thigh)
-skin - test site and untreated
-spinal cord
-spleen *
-sternum with marrow
-stomach
-testes *
-thymus *
-thyroid and parathyroid *
-trachea
-urinary bladder
-uterus w/cervix *

* included organ weight. Tissues preserved, but not examined included the bronchi, femur w/joint, salivary gland (submandibular), sciatic nerve, skin and tongue.

Summary of Study Results: Signs of reaction to treatment were limited to observation of pale feces in the animals treated with 2000 mg/kg/day (the result of unabsorbed test material in the feces). There were no significant differences between groups in bodyweight, food intake, blood and urine

profiles, and organ weights. No ophthalmic, macroscopic or microscopic pathological abnormalities were observed. The no effect level (NOEL) determined in this study was 2000 mg/kg/day.

Toxicokinetic Results: Dose related n-docosanol concentrations were detected in the plasma of all treated dogs but not in controls. As observed in rats, plasma concentrations of n-docosanol in dogs, characterized by C_{max} and AUC_{0-24}, were less than the proportionate dose increment and appeared tc be characterized by non-linear (dose-dependent) kinetics (Table TK-2). Inter-individual variation in plasma concentrations was high (coefficient of variation generally being greater than 50%, and in the range of [redacted] The time to maximum n-docosanol plasma levels (T_{max}) was also highly variable, with both intra- and inter-animals times ranging between 2 and 12 hours. The maximum n-docosanol plasma level (C_{max}) was 3 µg/ml in animals dosed at 2000 mg/kg/day.

Table TK-2: The mean maximum plasma concentration (C_{max}) of n-docosanol and the mean areas under the plasma n-docosanol concentration time curves estimated up to 24 hours post dose (AUC_{0-24}) on Day 1 and during Weeks 13 and 26 in Beagle dogs are summarized below, with standard deviations in parentheses.

A: C_{max} (ng/ml)

Dose	Day 1		Week 13		Week 26	
(mg/kg/day)	Males	Females	Males	Females	Males	Females
20	74 (50)	26 (10)	159 (91)	151 (44)	137 (53)	310 (205)
200	473 (244)	207 (93)	1841 (601)	1186 (854)	757 (388)	1289 (1020)
2000	1308 (326)	1469 (463)	2140 (272)	2860 (1077)	1094 (814)	2255 (718)

B: AUC_{0-24} (ng.h/ml)

Dose	Day 1		Week 13		Week 26	
(mg/kg/day)	Males	Females	Males	Females	Males	Females
20	610 (473)	177 (115)	1550 (1377)	1377 (449)	848 (434)	2031 (1073)
200	4419 (1856)	1781 (1166)	14370 (3755)	8425 (6533)	7435 (3575)	7799 (5492)
2000	11830 (3238)	15080 (7425)	22430 (2275)	27830 (8361)	12340 (9028)	24400 (8043)

Plasma concentrations of n-docosanol at 24 hours post-dose were generally below the limit of detection (<10 ng/ml) following administration of 20 mg/kg/day. At 200 and 2000 mg/kg/day, measurable levels were detected at most sampling times, especially following multiple days of dosing. There were no statistically significant differences in toxicokinetics between male and females.

Dose Verification: Analysis of 20% n-docosanol study suspensions by [redacted] resulted in levels ranging between [redacted] w/w n-docosanol during the study period.

Acute and Repeat Topical Toxicology Study Reviews

Study 29 - Acute Dermal Toxicity Study with LIDAKOL Cream in Rats. Study report no. [redacted] 255587, . *In life:* 10/25 to 11/8/89, conducted by [redacted] in accordance with OECD GLP guidelines.

Summary Results: Administration of 2000 mg/kg n-docosanol topically to Wistar rats (5 animals/sex) under occlusive dressings (20 % n-docosanol cream) did not result in any mortalities or drug related clinical signs of toxicity during a 15 day post-dosing observation period. Slight scaling was observed between days 3 and 7. There were no macroscopic findings observed at necropsy.

Study 30 - Primary Skin Irritation/Corrosion Study with LIDAKOL and LIDAKOL Placebo in the Rabbit (4-Hour Semi-Occlusive Application). Study report no. [redacted] 087547, *In life:* 11/17 to 11/20/92, Conducted by [redacted] in accordance with GLP guidelines (OECD and 21 CFR 58).

Study Design: Male and female New Zealand White rabbits (3/study, aged 14-15 weeks) were dosed with 50 mg n-docosanol (0.5 grams of 10 % LIDAKOL cream - formulation 3) to a 6 cm^2 area of intact shaved skin. The area was covered with a semi-occlusive dressing for 4 hours, then flushed with water. Placebo cream was applied to the opposite flank. Skin reaction was assessed for 7 days post-dosing on a grading scale of 0 to 8 where 0=non-irritating, 0.1-2.0 = mildly irritating, 2.1-5.0 = moderately irritating, and 5.1-8.0 = severely irritating.

Summary of Study Results: Application of the 10% n-docosanol cream resulted in very slight erythema with no edema to well defined erythema with slight edema. Reactions resolved within 24 to 48 hours after exposure. No staining of treated skin was observed. Comparable skin irritation was observed with the topical placebo applied to the opposite flank. Both n-docosanol 10% cream and the placebo were assigned primary irritation indices of 0.2 (mildly irritating) when applied to intact rabbit skin. No signs of systemic toxicity were observed during the study period.

Study 31 - Primary Skin Irritation Study with LIDAKOL Cream in Rabbits (4-Hour Semi-Occlusive Application). Study report no. [redacted] 225598, *In life:* 10/24 to 10/31/89, Conducted by [redacted] in accordance with OECD GLP guidelines.

Study Design: This study was designed similarly to Study 30, except a 20% n-docosanol cream formulation was used. Male and female New Zealand White rabbits (3/study, aged 14-15 weeks) were dosed with 50 mg n-docosanol (0.5 grams of 20 % LIDAKOL cream - formulation 3) to a 6 cm^2 area of intact shaved skin. There were no placebo or control animals used in this study. The area was covered with a semi-occlusive dressing for 4 hours, then flushed with water. Skin reaction was assessed for 7 days post-dosing on a grading scale of 0 to 8 where 0 = non-irritating, 0.1-2.0 = mildly irritating, 2.1-5.0 = moderately irritating, and 5.1-8.0 = severely irritating.

Summary of Study Results: Slight scaling was observed between days 3 and 7 in all animals treated with the 20 % n-docosanol cream. Local signs consisted slight erythema. No staining of treated skin was observed.

Study 32 - Primary Eye Irritation Study in with LIDAKOL in Rabbits. Study report no. 255600, *In life:* 10/24 to 10/27/89, conducted by in compliance with OECD GLP guidelines. LIDAKOL batch no. 7-143-6/28/89.

Study Design: Three New Zealand White rabbits (1 male and 2 females, ages 14 and 15 weeks, respectively) were administered a single dose (100 mg) of n-docosanol 10 % cream (formulation 1) in the conjunctival sac.

Summary of Study Results: n-Docosanol cream showed a primary irritation score of 0.25, reflecting a conjunctival redness grade of 1 (out of a maximum of 3) at the end of 1 hour observation. All other eye irritation scores were 0. There were no acute clinical symptoms, staining of the cornea or conjunctiva, or corrosion of the cornea at any time during the course of the study.

Study 33 - Primary Eye Irritation Study in with LIDAKOL™ Suspension in Rabbits. Study report no. 255622, *In life:* 10/24 to 10/27/89, conducted by in compliance with OECD GLP guidelines. LIDAKOL batch no. 7-143-6/28/89.

Study Design: This study was conducted as described for Study 255600 (#34 above), except that a 20 % n-docosanol suspension (100 mg) was instilled into the conjunctival sac of only 1 male rabbit (age 14 weeks).

Summary of Study Results: Findings were consistent with the preceding study, with a primary irritation score of 0.25 and no adverse reactions observed except for a conjunctival redness of grade 1 observed 1 hour post administration.

Study 34 - Screening for THE Eye Irritancy Potential Using the Bovine Eye / Chorioallanoic Membrane (BECAM) Assay with LIDAKOL Cream. Study report no. 170054. *In life:* 11/8 to 11/9/89, conducted by in compliance with OECD GLP guidelines. LIDAKOL batch no. 7-143-6/28/89.

This study was previously submitted under submission N001, dated 7/16/91, and reviewed by Dr. Lauren Black, HFD-530, review dated 8/26/91. Her review has been incorporated below:

The bovine eye assay is an in vitro assay to detect corneal damage resulting from the application of test compounds. Eyes were obtained from cows within 15 min of their slaughter; eyes with evidence of prior corneal damage were excluded from the assay. Eight eyes were placed in a plastic egg tray (above the water level) in a bath maintained at 37° degrees with a humid atmosphere. One negative control (saline

treated) and 2 positive control eyes (toluene and acetone) were used. Test article was applied for 30 seconds to the cornea of 5 eyes, followed by a saline rinse. 10 minutes later, damage was scored with reference to the following parameters: opacity (0-4), epithelial detachment (0, 2, 3, or 4), and epithelial integrity (0, 0.5, 1, or 1.5). Scores for the different types of damage were summed and average for the 5 treated eyes. An average score of 1.1 was seen for LIDAKOL, in line with other "slight irritants".

For the chorioallantoic membrane assay, the membrane was exposed in day 10 fertilized chicken eggs. Twelve eggs were used - 6, for test article; 2 eggs for negative control (saline), and 4 eggs for positive controls (sodium hydroxide and 1% SDS, 2 eggs each). A tenth of a gram of LIDAKOL cream was placed in contact with the surface of the membrane for 20 seconds, then rinsed. The capillary system and albumen were scored for hemorrhage, coagulation, and lysis. Scores were averaged and combined to yield a scale from 0-21. The positive control yielded scores of 11-19; the test article, 6.

The results of this assay showed LIDAKOL to be moderately irritating.

Study 35 - Acute Eye Irritation/Corrosion Study with LIDAKOL in the Rabbit. Study report no. [redacted] 107505. *In life:* 11/16 to 11/19/93, conducted by [redacted] in compliance with OECD GLP guidelines. LIDAKOL batch no. 153 (exp. date 6/1/94).

Study Design: The purpose of this study was to assess the possible irritation or corrosion potential when a single dose of LIDAKOL 10 % Cream was placed in the conjunctival sac of an albino rabbit eye (ages ~14 weeks). A single doses of 100 mg of n-docosanol 10 % cream was instilled into one eye each of 3 male rabbits. After 24 hours, both eyes were gently flushed with a solution of 2% fluorescein in water. The 2 % fluorescein allowed quantitative determination of corneal epithelial damage. Any bright green stained area, indicating epithelial damage, was estimated as a percentage of the total corneal area. The eyes of each animal were examined approximately 1, 24, 48 and 72 hours after instillation.

Summary of Study Results: Installation of LIDAKOL 10 % Cream resulted in slight irritation of the conjunctival tissues (conjunctival redness and chemosis, severity score = 1) at 1 hr in all three animals, which resolved within 48 hours. No signs of corneal epithelial damage or systemic toxicity were reported.

Study 36 - Contact Hypersensitivity to LIDAKOL Cream in Albino Guinea Pigs Maximization Test. Study report no. [redacted] 255611, *In life:* 12/12/89 to 1/5/90, conducted by [redacted] in compliance with OECD GLP guidelines.

Study Design: Himalayan spotted female guinea pigs (20 test and 10 control) received intradermal injections of Freund's complete adjuvant (CFA), n-docosanol 20 % (diluted to 5 % with ethanol), n-docosanol 20 % cream (diluted to 5 % with ethanol) with CFA, and vehicle at different sites. Intradermal injections (3 pairs/animal) were made at the border of a 4x6 cm area of shaved skin on each animal. Control groups were treated identically, with the omission of the test article, and substitution of ethanol. Six days after injections, 10 % SDS was applied to the shaved area to

enhance the appearance of any sensitization reactions. The next day, saturated filter patches of undiluted LIDAKOL were applied to the shaved area. An occlusive bandage was secured over the patch for 48 hours. Following this epidermal application, the area was washed and scored for erythema and edema immediately, 24, and 48 hours later. Two weeks following the epidermal application, an area on the right and left flanks of each pig was clipped, and filter patches saturated with LIDAKOL were applied to the right side, while ethanol soaked patches were secured to the left. Twenty-four hr later, the patches were removed, and the area washed and scored for reaction immediately, 24 and 48 hours later. Allergic reaction was scored "positive" if the challenge site was visibly reddened. In addition to skin reactions, mortality, body weights, and clinical symptoms were evaluated; no necropsy was performed. Formaldehyde (HCHO) was used as the positive control.

Summary of Study Results: No systemic symptoms were noted, nor were body weight gains affected by treatment with LIDAKOL. In this 25-day test, no differences attributable to test article were noted, with the exception of staining and fissures in the treated groups at the site of epidermal induction on day 11-15. No erythema was noted following challenge with LIDAKOL, indicating LIDAKOL is not sensitizing in this animal model.

Comment: Local symptoms at the injection sites were rather severe in both drug-treated and control groups. These included erythema and edema, days 2-6; necrosis, days 7-11; desiccation from days 11-16; and exfoliation, day 17-25.

Study 37 - Assessment of Contact Hypersensitivity to LIDAKOL in the Albino Guinea Pig (Maximization Test). Study report no. [redacted]107516, *In life:* 10/9/ to 12/4/93, conducted by [redacted] in compliance with OECD GLP guidelines.

Study Design: Guinea pigs were injected intradermally with a 25 % concentration of n-docosanol 10 % cream diluted in distilled water (20 animals) or physiological saline (10 animals). One week later, the animals were induced with an epidermal exposure to undiluted n-docosanol cream. Two weeks later, animals were challenged with n-docosanol 10% cream at concentrations of 25 %, 50 % and 100 % and with distilled water. Formaldehyde (0.05 to 0.2 %) was used as the positive control.

Summary of Study Results: 48 Hours after the occluded epidermal induction period, 8/20 animals presented with slight (1) to well defined (2) erythema, accompanied by slight edema in 3 of these animals. There were no positive reactions in any of the animals, at any dose in response to rechallenge. There were no signs of systemic toxicity observed in any of the animals and weight gain between control and treated animals was similar over the study period.

Study 38 - Phototoxicity Study of 10 % n-Docosanol Cream (LIDAKOL) in the Guinea Pig. Study report no. 95/LAK013/0038, *In life:* 12/7 to 12/14/94, conducted by [redacted] in compliance with GLP guidelines (OECD and 21 CFR 58). LIDAKOL and placebo batch nos. 153-93L and 152-93L, respectively.

Study Design: The potential of 10 % n-docosanol cream (LIDAKOL) to cause phototoxicity was investigated in Dunkin-Hartley guinea pigs (3/sex, 5-6 weeks of age). The backs of the animals (~6 cm^2) were clipped, depilated and stripped, and test material (0.5 ml) was applied to anterior and posterior sites (1.5 cm^2 each). Thirty minutes later, the posterior site was covered with [redacted] while the anterior site was irradiated with UVA light. Animals were evaluated at 1, 24, 48 hours and 7 days after treatment. Results were compared to concurrent control animals (3/sex/group) receiving either placebo cream or 0.01 % 8-methoxyposralen. The source of the irradiation was an array of [redacted] fluorescent tubes, monitored by a [redacted] (This system emitted primarily UVA radiation with small quantities of UVB.)

Summary of Study Results: There was no response for either the UVA-irradiated or the non-irradiated n-docosanol treated sites. There was slight to moderate erythema for both irradiated and non-irradiated placebo controls; exfoliation was apparent in 4/6 animals on day 8. Animals treated with [redacted] exhibited slight to moderate erythema and/or edema at 24 and 48 hours; by day 8, slight erythema, edema, eschar, exfoliation and a single case of scar tissue were apparent.

Study 39 - Photosensitivity Study of 10 % n-Docosanol (LIDAKOL) Cream in the Guinea Pig. Study report no. 95/LAK014/0260, *In life:* 1/16 to 2/23/95, conducted by [redacted] in compliance with GLP guidelines (OECD and 21 CFR 58). LIDAKOL batch no. 153-93L.

Study Design: [redacted]

Summary of Study Results: Test group animals challenged with 10 % n-Docosanol Cream showed no response at any of the non-irradiated or irradiated sites. After the fourth induction (day 8) there was a significant dermal reaction to TCSA which included exfoliation and a low incidence of eschar. Upon challenge with TCSA, 9/10 animals displayed slight erythema at the irradiated site. As expected, no reaction was observed at the TCSA non-irradiated sites. Slight to moderate erythema was observed in 5/10 of the negative control animals at the non-irradiated and/or irradiated challenge

sites treated with 10 % n-docosanol cream. The cause of this irritation is unknown, since all the test animals treated with 10 % n-docosanol cream throughout the study period were negative.

Study 40 - A 13-Week toxicity study by Dermal Application of n-Docosanol Cream (LIDAKOL®) to CD-1 Mice Including Toxicokinetic Assessments. Study Report no. 95/LAK018/0864, *In life:* 2/8 to 5/11/95, conducted by [redacted] with toxicokinetic sample analyses performed by [redacted] in compliance with OECD GLP guidelines. Test substance batch nos.: n-Docosanol 10 % Cream - GL017F-94L; Vehicle Control Cream - 318-09-95A.

Study Design: CD-1 mice (10/sex/toxicology group, 35-42 days of age) were treated topically with a cream containing 0.4, 2.0, and 10 % n-docosanol, vehicle cream, or water. The 0.4 and 2.0 % creams were made by diluting 10 % n-docosanol cream with water. Approximately 100 µl/day of cream or water was applied by syringe to the clipped back of the animals, estimated to be at least 10% of the total body surface area, and then spread evenly over the clipped area. Treatment sites were non-occluded. Before each administration, test sites were washed to remove any residual compound and examined for signs of irritancy. In addition, the following parameters were evaluated over the course of the study: mortality, clinical behavior (twice daily), bodyweight (weekly), food consumption (weekly), clinical hematology and chemistry (week 14), ophthalmoscopy (week 12), organ weights, and macroscopic and microscopic morphology. The following tissues were collected for histopathology (* included organ weight):

-adrenals *
-aorta
-brain *
-cecum
-colon
-duodenum
-epididymides
-esophagus
-eyes and optic nerves
-femoral bone including joint and marrow
-gall bladder
-harderian glands
-heart *
-ileum
-jejunum
-kidneys *
-liver *
-lungs w/mainstem bronchi *
-lymph nodes - axillary, mandibular and mesenteric
-mammary gland
-ovaries *
-pancreas
-pituitary *
-prostate *
-rectum
-salivary glands (submandibular)
-sciatic nerve (left)
-seminal vesicles
-skeletal muscle (thigh)
-skin - test site and untreated
-spinal cord
-spleen *
-sternum
-stomach
-testes *
-thymus *
-thyroid and parathyroid *
-tongue
-trachea
-urinary bladder
-uterus w/cervix *
-vagina

Satellite animals (16/sex/group) were dosed for toxicokinetic analysis on day 1. Blood samples were obtained from 2 animals/sex at 0, 0.5, 1, 2, 4, 6, 8, and 24 hours post-dosing. Each animals was sampled once and killed without recovery from anesthesia without necropsy. Following the final treatment in week 13, samples were collected from 8 animals/sex/treatment group as follows: each animal was sampled twice, once at 0 and 4 hours, 0.5 and 6 hours, 1 and 8 hours, or 2 and 24 hours post-dosing then sacrificed without necropsy.

Summary of Study Results: There were no deaths or clinical signs of toxicity which appeared to be dose-related. Bodyweight gain, food consumption, food conversion efficiency, organ weights, hematology, blood chemistry and the composition of the urine and bone marrow were unaffected by treatment. There were no ophthalmic, macroscopic or microscopic findings which were attributed to treatment with n-docosanol. 10 % n-Docosanol Cream was considered the NOEL in mice treated daily for 13 weeks on approximately 10 % of their total body surface area.